

Prediction of Heterogeneity in Intelligence and Adult Prognosis by Genetic Polymorphisms in the Dopamine System Among Children With Attention-Deficit/Hyperactivity Disorder

Evidence From 2 Birth Cohorts

Jonathan Mill, PhD; Avshalom Caspi, PhD; Benjamin S. Williams, BA; Ian Craig, PhD; Alan Taylor, MSc; Monica Polo-Tomas, MSc; Craig W. Berridge, PhD; Richie Poulton, PhD; Terrie E. Moffitt, PhD

Context: The study and treatment of psychiatric disorders is made difficult by the fact that patients with identical symptoms often differ markedly in their clinical features and presumably in their etiology. A principal aim of genetic research is to provide new information that can resolve such clinical heterogeneity and that can be incorporated into diagnostic practice.

Objective: To test the hypothesis that the *DRD4* seven-repeat allele and *DAT1* ten-repeat allele would prove useful in identifying a subset of children with attention-deficit/hyperactivity disorder (ADHD) who have compromised intellectual functions.

Design: Longitudinal epidemiologic investigation of 2 independent birth cohorts.

Setting: Britain and New Zealand.

Participants: The first cohort was born in Britain in 1994-1995 and includes 2232 children; the second co-

hort was born in New Zealand in 1972-1973 and includes 1037 children.

Main Outcome Measures: Evaluation of ADHD, IQ, and adult psychosocial adjustment.

Results: We present replicated evidence that polymorphisms in the *DRD4* and *DAT1* genes were associated with variation in intellectual functioning among children diagnosed as having ADHD, apart from severity of their symptoms. We further show longitudinal evidence that these polymorphisms predicted which children with ADHD were at greatest risk for poor adult prognosis.

Conclusion: The findings indicate that genetic information of this nature may prove useful for etiology-based psychiatric nosologies.

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Author Affiliations: Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College, London, England (Drs Mill, Caspi, Craig, and Moffitt, Messrs Williams and Taylor, and Ms Polo-Tomas); Department of Psychology, University of Wisconsin, Madison (Drs Caspi, Moffitt, and Berridge); and Dunedin School of Medicine, University of Otago, Dunedin, New Zealand (Dr Poulton).

PSYCHIATRY ASPIRES TO A diagnostic system based on knowledge of etiology and on objective diagnostic tests, as is typical of other medical disciplines.¹ Currently, psychiatric disorders are diagnosed on the basis of symptom syndromes only. However, psychiatric patients with identical symptoms are often found to differ markedly in associated clinical features, treatment response, prognosis, and presumably etiology. This heterogeneity undermines the value of psychiatric diagnosis. One aim of genetic research is to provide insight into the etiology of psychiatric disorders and contribute objective tests that augment diagnostic practice.² In this article, we present data from 2 cohort studies suggesting the possibility that genetic information

may eventually help to refine diagnosis and prognosis in one disorder notable for its heterogeneity: childhood attention-deficit/hyperactivity disorder (ADHD).

Attention-deficit/hyperactivity disorder is characterized by symptoms of hyperactivity, inattention, and impulsivity,³ but there is considerable variation in clinical features among children who meet diagnostic criteria for the disorder.⁴ Children diagnosed as having ADHD differ with regard to intellectual functioning,⁵ comorbidity with conduct disorder,⁶ and therapeutic response to stimulant drugs.⁷ This heterogeneity extends to long-term prognosis; some children's ADHD symptoms remit during adolescence, whereas other children's symptoms persist beyond adolescence.⁸ Moreover, some children with ADHD, but not others, are at

high risk for developing adjustment problems as adults, including antisocial behavior, substance abuse, psychiatric disorders, and difficulties in education and work.^{9,10}

Among the aforementioned features of heterogeneity within ADHD, the earliest to emerge is variation in intellectual ability. Several specific intellectual abilities are implicated in ADHD, including learning, memory, attention control, and other executive functions.¹¹ This article focuses on IQ as assessed by standardized tests, because it is a nonspecific yet reliable and valid index of the overall integrity of the brain's intellectual functions.¹² On average, children with ADHD score 7 to 12 IQ points lower than control children, but this average difference conceals enormous IQ variation within children with ADHD.^{13,14} The IQ may be key to understanding heterogeneity within ADHD because intellectual deficit has been associated with comorbid conduct disorder,^{11,15} poor response to stimulant treatment,¹⁶ and poor prognosis.^{17,18} Given the clinical significance of IQ in ADHD, the goal of this study was to investigate whether genetic polymorphisms previously associated with ADHD might be more specifically associated with intellectual variation within ADHD and thus prove useful in identifying a subtype of children with ADHD characterized by intellectual deficits.

Initial investigations have made progress in identifying genes implicated in the etiology of ADHD by targeting genes involved in monoamine neurotransmission.¹⁹ Although findings have not always been replicated, polymorphisms in 2 dopaminergic loci stand out as the most frequently replicated molecular correlates of ADHD.²⁰ First is the 7-repeat allele of a variable-number tandem repeat polymorphism in the dopamine D4 receptor gene (*DRD4*). Meta-analysis revealed a pooled odds ratio with ADHD of 1.45 (95% confidence interval [CI], 1.27-1.65) in case-control and 1.16 (95% CI, 1.03-1.31) in family-based association studies.²⁰ Second is the 10-repeat allele of a variable-number tandem repeat in the 3'-untranslated region of the dopamine transporter gene (*DAT1*). Meta-analysis revealed a pooled odds ratio with ADHD of 1.13 (95% CI, 1.03-1.24).²⁰

Following previous theorizing and research, we hypothesized that these polymorphisms may be helpful in differentiating between subgroups of children with ADHD. Specifically, we hypothesized that the *DRD4* seven-repeat allele and *DAT1* ten-repeat allele would prove useful in identifying a subset of children with ADHD who have compromised intellectual functions. Three lines of evidence suggested this hypothesis. First, the fact that associations between *DRD4* and *DAT1* and ADHD are small and inconsistent across samples could reflect heterogeneity in genetic etiology, suggesting the hypothesis that these dopamine system genes may be associated with a specific subset of children with ADHD.²¹⁻²³ Second, both the *DRD4* seven-repeat and the *DAT1* ten-repeat alleles have been associated with aspects of reduced dopaminergic transmission^{24,25}; dopamine is a powerful regulator of multiple aspects of cognitive functions,²⁶ and hypofunctioning dopamine systems are linked to compromised cognitive functions.²⁷ Third, a connection between *DRD4* and *DAT1* and intellectual functioning within ADHD is suggested by evidence that IQ and these 2 genes share similar connections with responsiveness to the most often prescribed treatment approach for ADHD: stimulant drugs (eg, methylpheni-

date or amphetamine). Specifically, there is suggestive evidence that lower IQ among patients with ADHD predicts poor drug response¹⁶; that carriers of the *DRD4* seven-repeat allele and homozygous carriers of the *DAT1* ten-repeat allele show poor drug response, although there are inconsistencies⁷; and that good ADHD response to stimulant treatment includes improved intellectual functioning.²⁸ Evidence that stimulant response, intellectual ability, and genotype may be correlated led us to hypothesize that polymorphisms in *DAT1* and *DRD4* may help explain heterogeneity in intellectual functioning in children with ADHD.

Although the aforementioned theorizing and findings allowed us to frame an a priori hypothesis, the evidence base behind this hypothesis is relatively indirect. Therefore, we required replication in 2 studies before reporting the findings in this article. Specifically, we report data from independent birth cohort studies in Britain and New Zealand. These cohorts are useful for this research because they faithfully represent population heterogeneity within controls and also within ADHD cases; the cases were not subject to factors that can yield biased recruitment into clinic-identified samples.²⁹ Herein we show replicated evidence that polymorphisms in the *DRD4* and *DAT1* genes are associated with variation in IQ scores in children with ADHD. We also report initial evidence that these polymorphisms predict which children with ADHD are at risk for poor adult prognosis.

METHODS

SAMPLES

Participants in the first cohort were members of the Environmental Risk Longitudinal Twin Study (E-Risk),³⁰ which tracks the development of a birth cohort of 2232 children. This E-Risk sample was drawn from a larger 1994-1995 birth register of twins born in England and Wales.³¹ The sample was constructed in 1999-2000, when 1116 families with same-sex 5-year-old twins participated in home visit assessments, forming the base cohort for the longitudinal E-Risk study. Details of sample construction are reported elsewhere.³⁰ Briefly, we used a high-risk stratification strategy to replace any families lost to the original register at the time of birth due to selective nonresponse, and we included a further high-risk oversample to ensure sufficient numbers of children with behavioral disorders for statistical power. All statistical analyses of data from the E-Risk cohort were weighted back to the population using information from Great Britain's General Household Survey.³² Thus, findings reported herein can be generalized to the general population of British families with children born in the 1990s. At the age 5 years assessment, with parents' permission, questionnaires were mailed to the children's teachers, who returned questionnaires for 94% of the children. Two years later, when the children were 7 years old, a follow-up home visit was conducted for 98% of the 1116 E-Risk families, and teacher questionnaires were obtained for 91% of the 2232 E-Risk twins (93% of those followed up). Because each study family contains 2 children, all statistical analyses in this report were corrected conservatively for the non-independence of the twin observations by using tests based on the sandwich or Huber-White variance estimator.³³

Participants in the second cohort were members of the Dunedin Study,³⁴ which tracks the development of a birth cohort of 1037 children. This sample was constructed when the investigators enrolled 91% of consecutive 1972-1973 births in Dunedin, New Zealand, when the children were 3 years old. Cohort fami-

Table 1. Protocol Summaries for Genotyping *DRD4* and *DAT1* Variable-Number Tandem Repeats*

Gene	Primer Sequences	Temperature, °C/PCR Conditions	Product Separation
E-Risk (Buccal DNA)			
<i>DRD4</i>	F: HEX-GGTCTGCGGTGGAGTCTG R: GCGACTACGTGGTCTACT	55	Capillary electrophoresis
<i>DAT1</i>	F: FAM-CCAGGCAGAGTGTGGTCTG R: GTGTAGGGAACGGCCTGAG	62	Capillary electrophoresis
Dunedin Study (Lymphocyte DNA)			
<i>DRD4</i>	F: GGTCTGCGGTGGAGTCTG R: GCGACTACGTGGTCTACT	55/Dimethyl sulfoxide and Hot-start <i>Taq</i>	2% Agarose
<i>DAT1</i>	F: TTGTGGTGTAGGGAACGGC R: CATTGCAAAACATAAAAACCTGTTGT	58/Hot-start <i>Taq</i>	2% Agarose

Abbreviations: E-Risk, Environmental Risk Longitudinal Twin Study; PCR, polymerase chain reaction.
*Further details are available from the authors.

lies represent the full range of socioeconomic status in the general population of New Zealand's South Island. Details about the sample are reported elsewhere.³⁴ Follow-ups have been performed at the ages of 5, 7, 9, 11, 13, 15, 18, 21, and most recently 26 years, when 96% of the living cohort members were assessed.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

In the E-Risk study, ADHD was ascertained on the basis of mother and teacher reports at the ages of 5 and 7 years (1999-2002).³⁵ In the mother interview, children's symptoms were assessed with 18 items concerning hyperactivity, impulsivity, and inattention, representing symptom criteria for ADHD specified by the *DSM-IV*³⁶ (eg, "very restless, has difficulty staying seated for long," "impulsive, acts without thinking," or "inattentive, easily distracted"). Symptoms were reported for the preceding 6 months. Teachers rated the same set of items. A research diagnosis of ADHD was made following *DSM-IV* criteria. Children received the diagnosis if they had 6 or more of the hyperactivity-impulsivity symptoms or 6 or more of the inattentiveness symptoms according to either mother or teacher report. In addition, the other rater had to indicate 2 or more symptoms to ensure pervasiveness across home and school. Onset before the age of 7 years was required. The prevalence of this research diagnosis of ADHD was 8% (70% male).

In the Dunedin Study, ADHD was ascertained on the basis of child, mother, and teacher reports. At the ages of 11, 13, and 15 years (1983-1988), children's symptoms were measured with the Diagnostic Interview Schedule for Children-Child version,³⁷ with a reporting period of 12 months at each age.³⁸⁻⁴⁰ Interviews were conducted by a psychiatrist or clinical psychologist in private standardized sessions. In addition, each child's parent and teacher completed ADHD symptom scales that were used to ensure pervasiveness of the symptoms and confirm onset of the disorder before the age of 7 years. A research diagnosis of ADHD was made based on the then-current *DSM-III*.⁴¹ The prevalence of this research diagnosis of ADHD was 6% (80% male).

CHILDREN'S IQ SCORES

In the E-Risk study, IQ was measured at the age of 5 years using a short form of the Wechsler Preschool and Primary Scale of Intelligence-Revised⁴² comprising vocabulary and block design subtests, following procedures described by Sattler.⁴³ The IQs ranged from 52 to 145 and were normally distributed. Because of the young age of the children and the rarity of drug treatment for ADHD in Britain in the 1990s, the E-Risk ADHD group can be considered virtually stimulant free at age 5 years IQ testing.

In the Dunedin Study, IQ was measured at the ages of 7, 9, 11, and 13 years with the Wechsler Intelligence Scale for Children-Revised,⁴⁴ as described by Moffitt et al.⁴⁵ We combined the IQ scores from the 4 assessments to form an overall score. The children's IQ scores ranged from 55 to 147 and were normally distributed. Because of the rarity of drug treatment for ADHD in New Zealand between 1979 and 1985 when IQ was tested, the Dunedin ADHD group can be considered virtually stimulant free at the time of IQ testing. The IQ scores were standardized to a mean \pm SD of 100 \pm 15 in each cohort for comparison purposes.

ADULT PSYCHOSOCIAL ADJUSTMENT

The Dunedin cohort has been followed up to the age of 26 years, enabling us to test whether genotype accounted for heterogeneity in the long-term prognosis of children diagnosed as having ADHD. At the age of 26 years, different research topics were presented as standardized modules (eg, psychiatric interview, partner-relationships interview, and socioeconomic interview), each administered by a different trained examiner in private rooms at the research unit. Court records of criminal convictions were searched. We report on a cumulative index of 10 adult adjustment problems (previously described by Moffitt et al⁴⁶): violent conviction record, nonviolent conviction record, substance dependence diagnosis, psychiatric diagnosis, evidence of aggression against partners, evidence of aggression against minors, no high school qualification, out-of-wedlock parenthood, government welfare benefits, and long-term unemployment.

DNA EXTRACTION AND GENOTYPING

In the E-Risk study, DNA was obtained via buccal swabs from 96% of participants. In the Dunedin Study, DNA was obtained from 97% of participants, 93% via blood and 7% via buccal swabs. (To avoid potential problems of population stratification, DNA from Dunedin cohort members of Maori origin was not included.) The *DRD4* and *DAT1* variable-number tandem repeats were genotyped using protocols given in **Table 1**.

The most common *DRD4* allele was the 4 repeat (65% in both cohorts), followed by the 7 repeat (19% in both cohorts) and 2 repeat (9% in both cohorts), similar to allele frequencies reported for other white samples.⁴⁷ Consistent with previous research, children were considered to be at risk if they were carriers of at least one 7-repeat allele (34% in the E-Risk study and 34.5% in the Dunedin Study). The *DRD4* genotype risk status was not significantly associated with ADHD in the E-Risk study ($\chi^2=0.24$; $P=.62$) or the Dunedin Study ($\chi^2=0.13$; $P=.72$).

The most common *DAT1* allele was the 10 repeat (74% in the E-Risk study and 76% in the Dunedin Study) followed by

Table 2. IQ Scores for Control Children and Children With ADHD, Further Defined by the Presence or Absence of the 7-Repeat Allele of the *DRD4* Gene and by the Presence or Absence of the *DAT1* 10/10 Genotype*

Cohort	No ADHD Diagnosis				ADHD Diagnosis			
	Low-Risk Genotype	<i>DRD4</i> Risk Only	<i>DAT1</i> Risk Only	<i>DRD4</i> and <i>DAT1</i> Risk	Low-Risk Genotype	<i>DRD4</i> Risk Only	<i>DAT1</i> Risk Only	<i>DRD4</i> and <i>DAT1</i> Risk
E-Risk (British)	101.6 (15.0) (n = 522)	102.5 (15.4) (n = 252)	99.9 (14.5) (n = 649)	99.9 (14.2) (n = 335)	94.9 (14.3) (n = 44)	93.0 (14.4) (n = 27)	92.1 (16.7) (n = 66)	86.7 (12.6) (n = 34)
Dunedin Study (New Zealand)	102.3 (13.1) (n = 207)	101.2 (14.9) (n = 107)	100.6 (13.6) (n = 277)	101.5 (12.9) (n = 154)	96.4 (12.7) (n = 15)	93.7 (26.5) (n = 5)	88.2 (13.2) (n = 18)	85.2 (12.7) (n = 11)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; E-Risk, Environmental Risk Longitudinal Twin Study.

*Data are presented as mean (SD). The mean (SD) IQ score was 100 (15).

the 9 repeat (25% in the E-Risk study and 23% in the Dunedin Study), similar to allele frequencies reported for white samples.⁴⁸ Consistent with previous research, children were considered to be at risk if they were homozygous for the 10-repeat allele (57% in the E-Risk study and 58.5% in the Dunedin Study). The *DAT1* genotype risk status was not significantly associated with ADHD in the E-Risk study ($\chi^2=1.30$; $P=.25$) or the Dunedin Study ($\chi^2=0.14$; $P=.71$).

STATISTICAL ANALYSIS

Multiple regression was used to test the central hypothesis of this study in 3 steps. First, we tested whether children who met diagnostic criteria for ADHD had lower IQ scores than children who did not meet criteria. Second, subsets of children with ADHD were defined by the presence or absence of the *DRD4* seven-repeat allele and by the presence or absence of the *DAT1* 10/10 genotype. Children with ADHD were scored 0 if they carried no genetic risk, 1 if they carried 1 genetic risk, and 2 if they carried both risks. The subsets were compared on IQ; in the E-Risk study we had greater than 90% power, and in the Dunedin Study we had 75% power to detect effects of medium-to-large magnitude. Third, we tested whether the lower IQ of the ADHD-diagnosed children with an at-risk genotype was an artifact of these children having more severe ADHD symptoms by examining the association between IQ and genotype risks after controlling for number of ADHD symptoms. All regression analyses controlled for sex. **Table 2** gives the descriptive statistics for the subsets of children in both cohorts. Diagnoses of hyperactivity, intelligence testing, and genotyping were performed by different personnel blind to the other study variables and to the hypothesis of this study.

RESULTS

STUDY 1

Data from the E-Risk cohort confirmed the previously reported association between ADHD and low IQ. Children who met diagnostic criteria for ADHD had significantly lower IQ scores (mean±SD, 90.9±15.5) than comparison children (mean±SD, 100.8±14.7) ($t_{1,1099}=6.98$; $P<.001$).

Next, subsets of children with ADHD were compared on IQ. Children with ADHD defined by the absence of genetic risk had a mean IQ of 94.9. In contrast, children with ADHD defined by the presence of the *DRD4* seven-repeat allele had a mean IQ of 89.3, and children with ADHD defined by the presence of the *DAT1* 10/10 genotype had a mean IQ of 90.0. There was a significant dose-response association between IQ and number of

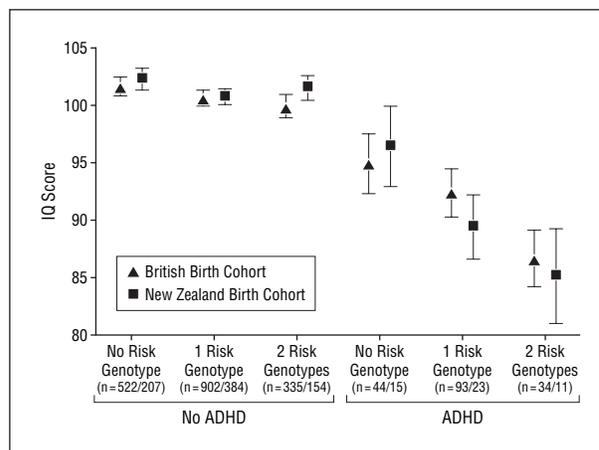


Figure 1. Mean±SE (error bars) IQ scores of control children and children who met diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) according to their genotype status on 2 dopamine genes. Data from 2 independent cohort studies in 2 countries show that children who met the diagnostic criteria for ADHD had significantly lower IQ scores than control children and that IQ variability among children with ADHD was explained by genotype.

genotype risks (0, 1, or 2 risks) ($b=-4.26$; $SE=1.77$; $t_{1,137}=2.40$; $P=.02$) (**Figure 1**). Children with ADHD with 1 risk (presence of either *DRD4* seven-repeat or *DAT1* 10/10 genotype) scored 2.6 IQ points lower than children with no risks, and children with both risks scored 8.2 IQ points lower than children with no risks. (Controlling for social class did not alter the association between IQ and number of genotype risks [$P=.02$].)

SUPPLEMENTAL ANALYSES FOR STUDY 1

We tested whether the lower IQ of children diagnosed as having ADHD who had an at-risk genotype was merely an artifact of greater severity of their ADHD. The ADHD genotype subsets did not differ from each other on number of symptoms of hyperactivity/impulsivity ($b=0.04$; $SE=0.20$; $t_{1,142}=0.19$; $P=.85$) or inattention ($b=0.29$; $SE=0.26$; $t_{1,142}=1.09$; $P=.28$) (**Table 3**). Moreover, the association between number of genotype risks and IQ among children diagnosed as having ADHD remained significant after controlling for number of symptoms of hyperactivity/impulsivity ($t_{1,137}=2.39$; $P=.02$) and inattention ($t_{1,137}=2.07$; $P=.04$).

After our a priori hypothesis that genotype would explain IQ variation in children with ADHD was tested in

Table 3. Symptom Severity as a Function of ADHD Diagnostic Grouping in 2 Birth Cohorts*

Cohort	No ADHD Diagnosis	ADHD Diagnosis		
		Low-Risk Genotype	1 Genotype Risk	DRD4 and DAT1 Risk
E-Risk (British)	n = 1763	n = 44	n = 96	n = 37
Hyperactivity symptom scale	.84 (.95)	4.6 (1.7)	4.5 (1.5)	4.7 (1.4)
Inattention symptom scale	0.50 (0.77)	3.8 (1.9)	3.9 (2.1)	4.3 (1.9)
Dunedin Study (New Zealand)	n = 745	n = 15	n = 23	n = 11
Hyperactivity symptom scale	1.7 (2.6)	5.2 (5.6)	5.7 (4.0)	5.5 (4.3)
Inattention symptom scale	1.2 (1.8)	5.2 (3.8)	4.2 (3.1)	4.8 (3.3)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; E-Risk, Environmental Risk Longitudinal Twin Study.

*Data are presented as mean (SD).

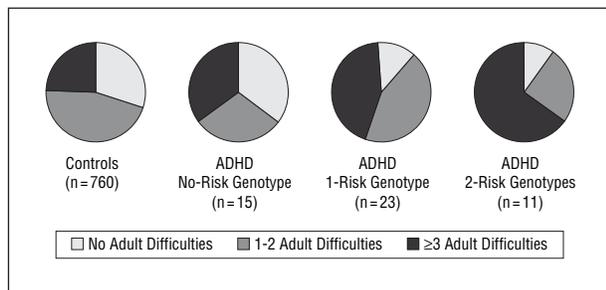


Figure 2. Adult prognosis of New Zealand children diagnosed as having attention-deficit/hyperactivity disorder (ADHD) varies with genotype. For each study member, 1 point each was summed for 10 different adult outcomes: a violent conviction record, a nonviolent conviction record, a substance dependence diagnosis, a psychiatric diagnosis, evidence of aggression against partners, evidence of aggression against minors, no high school qualification, out-of-wedlock parenthood, government welfare benefits, and long-term unemployment of more than 6 months. This longitudinal follow-up shows that children who met diagnostic criteria for ADHD had a worse adult prognosis than control children and that adult outcome heterogeneity among children with ADHD was explained by genotype.

the affirmative, we tested post hoc whether genotype would also predict comorbid conduct disorder, an important feature of ADHD heterogeneity^{49,50}; in this sample, 8% of children met diagnostic criteria for conduct disorder by the age of 7 years.⁵¹ The percentage of each genotype risk subset of children diagnosed as having ADHD who also developed conduct disorder was as follows: no-risk genotype group, 30%; 1-risk genotype group, 27%; and 2-risk group (*DRD4* and *DAT1*), 42%. This trend did not achieve statistical significance ($\chi^2=2.09$; $P=.35$).

We evaluated the possibility of an ethnic stratification artifact in which genetic risk might have characterized relatively more ethnic minority cohort members, who in turn might score lower on IQ tests. The relationship between genotype risk and IQ was reestimated excluding children from minority backgrounds with ADHD ($n=10$), yielding near identical results ($b=-4.24$; $SE=1.84$; $t_{1,128}=2.31$; $P=.02$).

STUDY 2

The results from the Dunedin cohort replicated those from the E-Risk cohort. Children diagnosed as having ADHD had significantly lower IQ scores (mean±SD, 90.6±14.9) than comparison children (mean±SD, 101.3±13.5) ($t_{1,793}=5.37$; $P<.001$). Next, subsets of children with ADHD were compared. Children with ADHD defined by the absence of genetic risk had a mean IQ of 96.4. In contrast, children with

ADHD defined by the presence of the *DRD4* seven-repeat allele had a mean IQ of 87.8, and children with ADHD defined by the presence of the *DAT1* 10/10 genotype had a mean IQ of 87.0. There was a significant dose-response association between IQ and number of genotype risks (0, 1, or 2 risks) ($b=-6.29$; $SE=2.71$; $t_{1,48}=2.32$; $P=.02$) (Figure 1). Children with ADHD with 1 risk (presence of either *DRD4* seven-repeat or *DAT1* 10/10 genotype) scored 7.0 IQ points lower than children with no risks, and children with both risks scored 11.2 IQ points lower than children with no risks. (Controlling for social class did not alter the association between IQ and number of genotype risks [$P=.03$].)

The Dunedin cohort has been followed up to the age of 26 years. Children diagnosed as having ADHD had worse adult outcomes than control children ($t_{1,807}=2.72$; $P=.007$). There was also a significant association between number of genotype risks (0, 1, or 2 risks) and adult outcomes among children with ADHD ($b=0.34$; $SE=0.16$; $t_{1,48}=2.12$; $P=.04$) (Figure 2). After controlling for IQ, this association was attenuated to nonsignificance ($P=.10$), indicating that the effect of dopaminergic risk genotypes on adult psychosocial adjustment was partly mediated by IQ deficits.

SUPPLEMENTAL ANALYSES FOR STUDY 2

The ADHD genotype subsets did not differ from each other on hyperactivity/impulsivity ($b=0.08$; $SE=0.91$; $t_{1,48}=0.09$; $P=.93$) or inattention ($b=-0.20$; $SE=0.67$; $t_{1,48}=0.29$; $P=.77$) symptoms (Table 3). Moreover, the association between number of genotype risks and IQ among children diagnosed as having ADHD remained significant after controlling for hyperactivity/impulsivity ($b=-6.40$; $SE=2.74$; $t_{1,48}=2.33$; $P=.02$) and inattention ($b=-6.38$; $SE=2.74$; $t_{1,48}=2.33$; $P=.03$) symptoms.

We tested post hoc whether genotype would also predict comorbid conduct disorder. Conduct disorder was ascertained using the procedures followed for ADHD; 20% met diagnostic criteria for conduct disorder between the ages of 11 and 18 years.³⁴ The percentage of each genotype risk subset of children diagnosed as having ADHD who developed conduct disorder was as follows: no-risk genotype group, 60%; 1-risk genotype group, 56%; and 2-risk group (*DRD4* and *DAT1*), 82%. This trend did not achieve statistical significance ($\chi^2=2.15$; $P=.34$).

After our a priori hypothesis that genotype would explain IQ variation in children with ADHD was tested in the affirmative, we tested post hoc whether this finding

had specificity to ADHD. We tested whether *DAT1* and *DRD4* genotype would explain IQ variation in children diagnosed as having anxiety disorders; like ADHD, anxiety disorders are associated with elevated arousal,⁵² and IQ deficit has been reported for children diagnosed as having anxiety disorders.⁵³ In the Dunedin Study, phobias, separation anxiety disorder, and overanxious disorder were ascertained at the same ages using the procedures followed for ADHD; 20% met diagnostic criteria for an anxiety disorder between the ages of 11 and 15 years.⁵⁴ Children with an anxiety disorder had a significantly lower IQ (mean±SD, 96.7±14.3) than nonanxious children (mean±SD, 101.8±13.4) ($t_{1,792}=4.24$; $P<.001$). However, in children diagnosed as having anxiety, genotype was not significantly associated with IQ ($b=-0.79$; $SE=1.61$; $t_{1,158}=0.48$; $P=.63$) (no-risk genotype group [$n=46$], mean±SD IQ, 98.0±13.0; 1-risk genotype group [$n=81$], mean±SD IQ, 95.9±15.7; *DRD4* and *DAT1* risk group [$n=32$], mean±SD IQ, 96.7±12.5). We could not perform this analysis in the E-Risk cohort because anxiety disorders were not diagnosed in 7-year-old children.

COMMENT

Data from 2 independent birth cohorts showed that polymorphisms in the dopaminergic genes *DRD4* and *DAT1* accounted for much of the heterogeneity in intellectual ability in children diagnosed as having ADHD. **Figure 3** summarizes the results according to the IQ bell curve. Superimposed on the curve are the results showing (1) IQ differences between children diagnosed as having ADHD vs children who did not meet ADHD diagnostic criteria and (2) IQ differences within the group of children diagnosed as having ADHD as a function of their genotypic risk. Two features of the findings warrant comment.

First, the within-group IQ difference is the same magnitude as the between-group IQ difference. In both instances the IQ difference spans 8 to 11 IQ points (or 0.5 to 0.75 SD) and corresponds to a moderate-to-large effect size. Such IQ differences are associated with important life outcomes.⁵⁵ Second, the findings are reproducible in 2 samples. Psychiatric genetics has been “mired in nonreplications,”^{56(p618)} revealing many initial association findings to be false-positive results. What precautions should be taken? Replication is the “sine qua non for accepting a hypothesis.”^{57(p627)} In the present study, the replication requirement was met by confirming the hypothesized finding in 2 independent, well-characterized birth cohorts, and the combined effect size across the 2 studies yielded $P=.003$. The similarity of the findings was notable in that the 2 cohorts were born in different eras (1970s vs 1990s), were diagnosed as having ADHD at different ages (5-7 years vs 11-15 years), were tested for IQ at different ages (5 years vs 7-13 years), and lived in different countries (Britain vs New Zealand), albeit countries with similar white ethnic origins. In addition, in the Dunedin Study, prospective longitudinal analyses revealed that the dopaminergic risk genotypes of children diagnosed as having ADHD could predict their adult psychosocial adjustment more than 10 years later, and this effect was mediated by their IQ deficits. This finding requires replication.

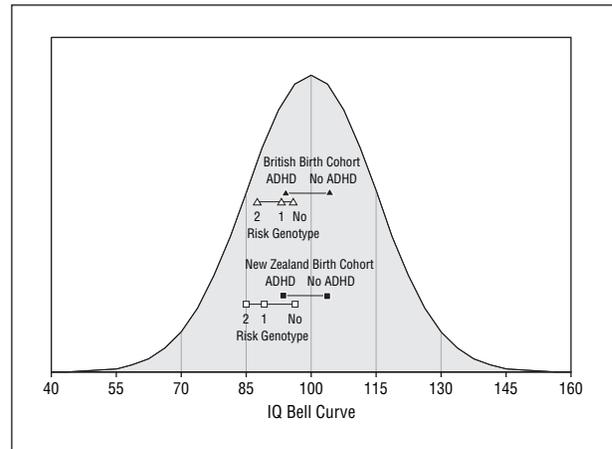


Figure 3. Children's IQ scores plotted on the bell curve as a function of attention-deficit/hyperactivity disorder (ADHD) diagnosis and genotype risk. The results show that the within-ADHD group difference as a function of genotype risk is similar in magnitude to the difference in IQ between children diagnosed as having ADHD and children not meeting ADHD diagnostic criteria.

Five points are relevant for interpreting these findings. First, the obtained relationship between genotype and IQ in children diagnosed as having ADHD was independent of the severity of each child's ADHD symptoms in both cohorts. This independence attests that this genotype-IQ relationship is not an artifact that arose because genetic risk produced more severe ADHD symptoms, which in turn disrupted the children's test taking. Second, although we did not have statistical power to separately analyze DSM-IV hyperactive vs inattentive diagnostic subtype groups, separate analyses attested that the genotype-IQ relationship was independent of symptom severity for both the hyperactive-impulsive and inattentive symptom syndromes. Third, drug treatment of ADHD was virtually nil in both cohorts when IQ was tested. This attests that the genotype-IQ relationship is unlikely to be an artifact that arose because the low-risk genotype promoted drug response, which in turn enhanced the successfully treated children's intellectual abilities. Fourth, the genotype-IQ relationship is unlikely to be an artifact that arose because of ethnic stratification in which genetic risk characterized more ethnic minority cohort members, who in turn might score lower on IQ tests. The Dunedin Study excluded cohort members of Maori origin, and the E-Risk study findings remained unaltered whether or not ethnic minority children with ADHD were excluded. Fifth, the dopaminergic polymorphisms predicted IQ deficits with specificity to children diagnosed as having ADHD. Analyses attested that genotype did not predict IQ among children affected with anxiety disorders, which are also characterized by hyperarousal.

The findings reported herein bring up several issues regarding the genetics of ADHD and, more generally, about subphenotyping complex behavioral disorders. First, the present findings may shed some light on the role of *DRD4* and *DAT1* in the pathogenesis of ADHD. The remarkable effectiveness of drugs that, in part, target dopaminergic neurotransmission originally implicated this system in the pathogenesis of ADHD⁵⁸ and pointed molecular investigations toward dopamine system candidate genes, including *DRD4* and *DAT1*. However, association studies of these genes have yielded mixed results,¹⁹ and genome-wide link-

age studies of ADHD have indicated that neither candidate gene likely plays a major role in the disorder.^{59,60} One explanation of such ambiguous findings is that there is genetic heterogeneity in ADHD. Therefore, these genes may not operate as pure susceptibility genes that increase the risk of ADHD (or of low IQ). Rather, they may influence phenotypic variation in ADHD and thus are associated with a specific subset of children with ADHD who have compromised intellectual functions. In keeping with this notion, we found that only in children diagnosed as having ADHD, an increasing number of risk genotypes was correlated with a lower tested IQ. That the genotype-IQ relationship was conditional on ADHD diagnosis suggests that the involvement of these 2 genes in ADHD relies on interactions with other genes or other etiological factors to influence a subtype of ADHD (and hence the genotype-IQ association was not observed among children without ADHD). Such a situation is anticipated by animal research showing that genetic variants are associated with highly variable phenotypes depending on genetic background (eg, knockouts lead to different phenotypic effects in different strains).⁶¹ The *DAT1* and *DRD4* polymorphisms may operate as modifier genes,⁶² acting against a background of other etiological factors, to affect clinical features and course of ADHD rather than as direct susceptibility genes affecting the disorder per se.

Second, the findings suggest one possible reason for between-study heterogeneity in candidate gene studies of ADHD focusing on *DRD4* and *DAT1*. The possibility that *DRD4* and *DAT1* operate as modifier genes implies that differences in sample characteristics may account for disparate research findings. There are large variations in intellectual ability across ADHD samples. Studies that contain ADHD cases with low IQ may observe significant associations, whereas studies that contain ADHD cases with relatively high IQ may fail to observe associations. Selective participation in community samples and referral biases in clinical samples may produce such sample differences and inadvertently contribute to between-study heterogeneity in molecular genetics research. Molecular genetic studies are beginning to explore phenotypic heterogeneity in ADHD as a possible source of between-study heterogeneity,²⁰ and the present findings nominate neurocognitive heterogeneity as a promising lead.⁶³

Third, the present findings suggest that ADHD may consist of subgroups that can be differentiated according to their genetic makeup. In particular, the findings encourage more focused attention on the additive and/or interactive pathophysiological effects of *DRD4* and *DAT1* on ADHD. Both the *DRD4* seven-repeat allele and the *DAT1* ten-repeat allele have been associated with aspects of reduced dopaminergic neurotransmission. The 7-repeat allele is associated with reduced sensitivity to dopamine.²⁴ Additionally, several studies suggest that the 10-repeat allele of *DAT1* increases dopamine transporter density, thus increasing the reuptake of synaptic/extracellular dopamine.²⁵ Through these actions and, as noted herein, by interacting with a background of general dopaminergic dysfunction present in children with ADHD, the co-occurring *DRD4* and *DAT1* risk polymorphisms could produce an extreme hypodopaminergic state, which may be correlated with poor cognitive function.²⁶ However, it is possible that the variants we stud-

ied are not the consequential polymorphisms but are in linkage disequilibrium with other nearby functional variants. In any event, this scenario illustrates one possible mechanism by which children with ADHD carrying these genotypes might form a cognitively distinct group with a differential prognosis. Our research was unfortunately limited by relying on omnibus IQ scores to measure neurologic integrity. Future research must go further to apply neuropsychological assessments and neuroimaging methods to reveal the specific brain functions involved and to ascertain whether the genotype-related IQ differences observed herein reflect global cognitive deficiencies or specific deficits that affect IQ.⁵

This study provides one example of how genetic information may in the future be able to resolve clinical heterogeneity and thus help to refine psychiatric diagnoses.⁶⁴ Clinical implications are premature, pending more widespread replication tests. However, our findings illustrate how genetic information may eventually be incorporated into psychiatric nosology through biomarker testing and a better understanding of pathogenesis.

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Correspondence: Terrie E. Moffitt, PhD, Institute of Psychiatry, SGDP Centre P080, De Crespigny Park, London SE5 8AF, England (t.moffitt@iop.kcl.ac.uk).

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